Prognostic Significance of Vascular Endothelial Growth Factor Protein Levels in T1-2 N0 Laryngeal Cancer Treated With Primary Radiation Therapy

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BACKGROUND. The purpose of this study was to assess the prognostic value of vascular endothelial growth factor protein levels in a large cohort of patients with T1-T2 N0 laryngeal cancer treated with primary radiation therapy (XRT).

METHODS. Primary tumor specimens from a cohort of 123 patients with T1-T2 N0 laryngeal cancer treated with XRT between 1975 and 2000 were constructed into a tissue microarray. Clinical prognostic factors included age, sex, T classification, and tumor subsite. Molecular prognostic factors included vascular endothelial growth factor, epidermal growth factor receptor, and p53 expression, determined by using immunohistochemistry on tissue microarrays. The association between vascular endothelial growth factor status, covariables, and outcome was assessed.

RESULTS. With a median follow-up of 9.9 years, 32 (26%) were diagnosed with local relapse (5-year local relapse-free rate, 70.4%). T2 tumor stage (31.7%) was a significant predictor of local relapse (relative risk [RR], 1.71; 95% confidence interval [CI], 1.21–2.43; P = .05). Positive expression of vascular endothelial growth factor, epidermal growth factor receptor, and p53 were: 8.5%, 58.7%, and 36.4%, respectively. In univariate analysis, vascular endothelial growth factor positivity was a significant predictor of overall survival (RR = 1.62; 95% CI, 0.99–2.42; P = .05). In multivariate analysis, positive vascular endothelial growth factor status maintained significant correlation with overall survival (RR, 2.79; 95% CI, 1.49–4.95; P = .002).

CONCLUSIONS. Vascular endothelial growth factor positivity appeared to be a significant predictor of overall survival in a multivariate model. Further evaluation of vascular endothelial growth factor-positive laryngeal cancers treated with primary XRT is warranted.


KEYWORDS: head and neck cancer, vascular endothelial growth factor, VEGF, radiation therapy, prognosis, P53.

In 2006, an estimated 9510 new diagnosis and 3740 deaths will occur from laryngeal cancer in the United States.1 An analysis performed on the National Cancer Data Base (NCDB) for cases of head and neck cancer registered between 1985 and 1995 found the most common head and neck cancer reported in the United States was laryngeal cancer, accounting for 20.9% of the 295,022 total cases.2 Definitive radiation therapy is the mainstay of treatment for early stage disease (T1-2 N0), which accounts for 50% to 60% of reported cases of laryngeal cancer.3,4 The goals of treatment for early laryngeal cancer are cure and voice preservation.5 Five-year local recurrence rates for T1 lesions are 5% to 20%, accounting for the primary cause of failure in these patients.4,6 Nevertheless, overall control of disease may reach 90% to 100% if surgical salvage is performed.7,8
Currently available clinicopathologic markers, such as extension of disease into nearby structures, lymph node status, and positive surgical margins, are suitable for predicting prognosis. Molecular markers have the potential to consistently select high-risk patients and label biologically aggressive disease. There has been considerable effort to explore molecular markers that predict local relapse and overall survival in laryngeal carcinoma; several markers that may develop into targets for novel adjuvant agents include: p53, cyclin D1, epidermal growth factor receptor (EGFR), and vascular endothelial growth factor (VEGF). A study by Cho et al. demonstrated the significance of COX-2 and Ki67 in the prognosis of a comparable cohort of patients with early, T1-2 N0 laryngeal cancer.

The macroscopic growth of tumors is partly due to proliferation of existing endothelium, a process known as angiogenesis. VEGF plays a key role in mediating this phenomenon by promoting endothelial cell proliferation and vascular permeability. Therefore, angiogenesis and subsequent tumor growth potential can be directly measured by expression of such factors (eg, VEGF) or the density of microvessels supplying the tumor. VEGF is a 34-50-kD dimmer comprising 2 identical disulfide-linked subunits from differential splicing of a single gene. VEGF is induced under hypoxic conditions in several tissue types and binds to tyrosine kinase receptors Fly-1 and KDR/Flk-1 to stimulate angiogenic factors. Those tissues that overexpress VEGF may be associated with portions of tumors that are biologically radioresistant and correlate with poor local control and overall survival. In 2000, Smith et al reported VEGF expression as an independent risk factor for poor local and overall survival in head and neck squamous cell carcinoma (HNSCC). A recent meta-analysis of HNSCC patients by Kyzas et al revealed that the risk of death in 2 years was almost 2-fold higher in VEGF-positive patients.

The purposes of this study were to assess the prognostic value of VEGF protein levels in a large cohort of patients with T1-T2 N0 laryngeal cancer who had been treated with primary radiation therapy and to correlate our findings with other clinicopathologic parameters.

MATERIALS AND METHODS

Patients

Patients diagnosed with T1-2 N0 squamous cell carcinoma of the glottic and supraglottic larynx and treated at the Department of Therapeutic Radiology, Yale University School of Medicine between 1975 and 2000 met inclusion criteria for this study. Of these patients treated with primary radiation therapy, 123 had archived tumor specimens available for analysis. Patients’ charts were reviewed and information on demographics, radiation therapy parameters, and tumor staging was obtained. Staging was performed in accordance with the American Joint Commission on Cancer (AJCC) Staging Manual. Patients were followed for a median of 9.9 years, with 16 patients lost to 5-year follow-up. All but 2 patients were clinically disease-free at the time of their loss to 5-year follow-up, and all were censored at this time. The protocol was reviewed and approved by the institutional review board.

Radiation treatment parameters as follows: bilateral laryngeal opposed wedged fields using beam energies ranging from 2 to 6 MV, 5 fractions per week, without planned treatment breaks. Patients were treated with a median daily fraction of 200 cGy (range, 180–255 cGy) to a total median dose of 66 Gy (range, 49.5–79 Gy) over 47 days (range, 27–78 days).

Immunohistochemical Analysis of Tissue Microarray for Expression of VEGF, EGFR, and p53

A tissue microarray was constructed for this analysis. A pathologist examined hematoxylin and eosin-stained slides of the archived paraffin blocks and circled representative tumor sections. From these tumor sections, two 0.6 mm cores were extracted using a Tissue Microarrayer (Beecher Instruments, Silver Spring, MD). The minimal percentage of the total specimen represented by the cores varied from 10% for the larger supraglottic specimens to 90% for the smaller glottic specimens. Sections of the microarrays 5 μm thick were cut with a tape-based tissue transfer system (Intrumedics, Hackensack, NJ) and processed as described previously. The representativeness of the tissue microarray biopsies has been previous validated in a variety of tumors, including head and neck, colorectal, and lung. The EGFR antibody has been validated in previous studies by using immunohistochemistry and Western blot analysis of normal and neoplastic tissue.

Immunohistochemical analysis was performed on 5-μm-thick tissue sections prepared from formalin-fixed, paraffin-embedded archival tissue from the resected primary tumor. Tissue sections were deparaffinized and then quenched in 2% hydrogen peroxide–methanol solution. Samples stained for VEGF were pretreated by microwaving them 3 times at 50% power for 5 minutes in 10-mmol/L sodium citrate (pH 6.0). Samples stained for EGFR were pretreated with 0.4% pepsin in 0.1% hydrochloric acid for 15 minutes at 37°C. Samples stained for p53 did not require an antigen retrieval step. Slides were incubated overnight at 4°C with the following antibodies, 1) a mouse monoclonal IgG1 reactive with the 34-kd to 50-kd isoforms of VEGF (1:200 dilution, clone JH121; Oncogene Research
Products, Cambridge, Mass); 2) a mouse monoclonal IgG2b reactive with wild-type and mutant forms of p53 (1:50 dilution, clone DO-7; DAKO, Carpentaria, Calif); and 3) a mouse monoclonal IgG1 antibody specific for the protein portion of the extracellular domain of EGFR (prediluted, clone E 30; BioGenex, San Ramon, Calif), incubated with the chromogen diaminobenzidine tetrahydrochloride, counterstained with hematoxylin, and mounted.

Assessment of VEGF, EGFR, and p53 staining was qualitative and done by an experienced pathologist who was blinded to patient outcome. For each core, the region of predominant staining intensity was scored. VEGF staining intensity was scored as 0 (none), 1+ (faint or focal), 2+ (moderate), 3+ (strong), and percentage distribution. For cores that were not interpretable because of tissue loss or lack of tumor cells, a score of not applicable (N/A) was given. Immunohistochemical staining for EGFR was assessed similarly to VEGF as stated above. Assessment of p53 staining was also similar to VEGF and EGFR, except that only nuclear reactivity was scored. For p53, <20% nuclear reactivity in tumor cells was scored as 1 (low p53 expression), and ≥20% nuclear reactivity was scored as 2 (high p53 expression).

The study endpoints were local relapse and overall survival, including all deaths. Time to local relapse was defined by biopsy-proven relapses in the glottic or supraglottic larynx. Both endpoints were calculated from the date of radiation therapy completion, as this represents the start of continuous risk for relapse. In addition, data were censored after 5 years to calculate 5-year statistics and to minimize random censoring because of loss of follow-up. The last recorded follow-up date was February 11, 2003. Median follow-up was calculated by the reverse Kaplan-Meier method. The independent variables for this analysis included age, sex, race, T classification, tumor subsite, VEGF expression, EGFR expression, and p53 status. Age was treated as a continuous variable after linearity assessment.

### Statistical Analysis

VEGF status and relevant covariates were assembled in a database and analyzed by using SAS User's Guide, Version 9.1 (SAS Institute, Cary, NC). All tests of statistical significance were 2-sided. *P*-values <.05 were considered statistically significant. Follow-up time and time to recurrence were calculated from the date of radiation to the date of the relevant outcome. Disease-free survival was calculated as the interval between the date of radiation and the date of first recurrence of disease.

### RESULTS

#### Descriptive Statistics

With a median follow-up of 9.9 years, a total of 32 (26.0%) patients experienced local relapse, for a 5-year actuarial local recurrence-free rate of 70.4%. The 5-year actuarial overall survival rate for the entire cohort was 60.2%, with 44 deaths during the follow-up period. Of the 44 deaths, only 5 patients died from local relapses, and the others died with no evident disease. Table 1 summarizes the clinicopathologic characteristics.

#### Table 1: Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Median ± SD 64.0 ± 10.9</td>
</tr>
<tr>
<td>Range</td>
<td>38-90</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 106 (86.2)</td>
</tr>
<tr>
<td></td>
<td>Female 17 (13.8)</td>
</tr>
<tr>
<td>Race</td>
<td>White 111 (90.2)</td>
</tr>
<tr>
<td></td>
<td>Black 12 (9.8)</td>
</tr>
<tr>
<td>T stage</td>
<td>T1 84 (68.3)</td>
</tr>
<tr>
<td></td>
<td>T2 39 (31.7)</td>
</tr>
<tr>
<td>Tumor subsite</td>
<td>Glottic 98 (79.7)</td>
</tr>
<tr>
<td></td>
<td>Supraglottic 25 (20.3)</td>
</tr>
<tr>
<td>VEGF status</td>
<td>Positive 9 (8.5)</td>
</tr>
<tr>
<td></td>
<td>Negative 97 (91.5)</td>
</tr>
<tr>
<td>EGFR status</td>
<td>Positive 54 (58.7)</td>
</tr>
<tr>
<td></td>
<td>Negative 38 (41.3)</td>
</tr>
<tr>
<td>p53 status</td>
<td>Positive 43 (36.4)</td>
</tr>
<tr>
<td></td>
<td>Negative 75 (63.6)</td>
</tr>
</tbody>
</table>

SD indicates standard deviation; VEGF, vascular endothelial growth factor; EGFR.
of the patient cohort including demographics, staging, and molecular marker status. Positive expression of VEGF, EGFR, and p53 were 8.5%, 58.7%, and 36.4%, respectively.

VEGF-positive staining intensities of 0, 1+, 2+, and 3+ were: 13 (12.2%), 34 (32.2%), 50 (47.1%), and 9 (8.5%), respectively. In accord with analysis parameters as above, the 9 strongly stained samples (8.5%) were defined as VEGF-positive, and the remaining 97 (91.5%) as VEGF-negative tumors. The median percentage of tumors reactive to VEGF antibody in those tumors labeled as VEGF-positive was 25%, with a minimum of 10%. Those tumors that were sufficiently immunoreactive with the VEGF antibody showed cytoplasmic granular staining, and the negative controls showed no staining. For the 92 cores stained for EGFR expression, positivity was defined as a staining intensity greater than 0.0, which was observed in 54 (58.7%) of 92 total cases. For p53, only nuclear localization of immunoreactivity was evaluated. The p53-overexpressed phenotype was defined as ≥20% nuclear reactivity with 43 (36.4%) of 118 cores positive.

Chi-Square Analysis
By using chi-square analysis and Fisher exact test, VEGF positivity was significantly associated with T classification (P = .02). As seen in Table 2, VEGF positivity did not correlate with any other molecular marker status, such as EGFR or p53 expression. Other prognostic variables, such as age, sex, race, and tumor subsite, were not significantly associated with the VEGF-positive phenotype.

Univariate Analysis
As depicted in the univariate analysis in Table 3, T2 stage was a significant predictor for 5-year local relapse (RR, 1.71; 95% CI, 1.21–2.43; P < .05). VEGF-positive phenotype was not a statistically significant predictor for local relapse (RR, 1.32; 95% CI, 0.64–2.24; P = .40), but it did predict poor overall survival (RR = 1.62; 95% CI, 0.99–2.42; P = .05). Kaplan-Meier survival curves for local recurrence-free survival and overall survival with respect to VEGF status are presented in Figure 1 and Figure 2, respectively. According to log-rank statistical methods used for local recurrence, there was no significant association with VEGF status—with 22.6% of VEGF-negative tumors (22 of 97 tumors) versus 33.3% of VEGF-positive tumors (3 of 9 tumors) recurring locally. As shown in Figure 1, the 5-year local recurrence-free survival for VEGF-negative tumors was
approximately 81% versus 59% for VEGF-positive tumors. Although there was a trend toward higher local relapse rates in VEGF-positive tumors, the difference did not reach statistical significance. Overall survival data at the 10-year mark (Fig. 2) indicate 31% survival for VEGF-negative patients versus only 13% survival for VEGF-positive patients (P = .02, log-rank test).

For 5-year poor overall survival, only age, T2 stage, and VEGF positivity were significant predictors (Table 3). In this cohort, age >59 years predicted worse 5-year overall survival (RR = 1.41; 95% CI, 1.00–2.09; P = .04). T2 stage predicted a relative risk of about 1.5 times that of T1 stage for poorer overall survival (95% CI, 1.10–2.00; P < .05). In addition, an EGFR-positive phe-

notype was not a good predictor of local recurrence rates (RR = 0.07; 95% CI, 0.47–1.04; P = .07) or overall survival (RR = 0.84; 95% CI, 0.59–1.19; P = .31). In 36.8% of patients with EGFR-negative tumors (14 of 38 tumors), tumors recurred locally; whereas in 20.3% of patients with EGFR-positive tumors (11 of 54 tumors), tumors recurred locally. Also, p53 failed to demonstrate significant association with local relapse rate (RR = 1.03; 95% CI, 0.70–1.58; P = .88) or overall survival (RR = 0.94; 95% CI, 0.68–1.32; P = .71).

Multivariate Analysis

Multivariate survival estimates were based on the Cox proportional hazards model and assumed no interactions between significant variables in the final model. VEGF status and other covariables such as age, sex, and T classification were entered into this multivariate model to determine their relation with local recurrence rates and overall survival. On analysis seen in Table 4, T2 stage maintained prognostic significance with relation to local recurrence (RR = 1.70; 95% CI, 1.02–2.75; P = .04) and overall survival (RR = 1.47; 95% CI, 0.99–2.11; P = .05). Although not significant, VEGF positivity demonstrated a relative risk of 1.20 (95% CI, 0.46–2.46; P = .66) for local recurrence. Overall, patients with VEGF-positive status trended to recur 1.2 times more often when compared with patients of VEGF-negative status.

For overall survival, the parameters of age, sex, T classification, and VEGF status were entered into the final model. VEGF positivity entered the final model as an independent predictor. An age of older than 59 years remained a significant predictor of overall survival on

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**TABLE 4**

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Local recurrence</th>
<th>Overall survival</th>
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<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>1.03 (0.64–1.68)</td>
<td>1.63 (1.13–2.47)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1.50 (0.76–3.87)</td>
<td>1.41 (0.82–2.69)</td>
</tr>
<tr>
<td>T stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>1.70 (1.02–2.75)</td>
<td>1.47 (0.99–2.11)</td>
</tr>
<tr>
<td>VEGF status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1.20 (0.46–2.46)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
</tbody>
</table>

RR indicates risk ratio; CI, confidence intervals; Ref, reference group.
* Statistically significant.

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**FIGURE 1.** Effect of VEGF status on 5-year local recurrence (LR) rates for patients with T1-2 laryngeal tumors treated with primary RT. The 5-year LR-free survival was 81% for VEGF-negative tumors and 59% for VEGF-positive tumors (P = .36, log-rank test).

**FIGURE 2.** Effect of VEGF status on 10-year overall survival (OS) for T1-2 glottic tumors treated with primary RT. The 10-year OS was 31% for VEGF-negative tumors and 13% for VEGF-positive tumors (P = .02, log-rank test).
the basis of follow-up data \((P = .009)\). It was noted that the relative risk of poor overall survival with a positive VEGF phenotype increased from the univariate value of 1.62 to the multivariate value of 2.79 (95% CI, 1.49–4.95; \(P = .002\)) and remained significant. Thus, patients with VEGF-positive status were approximately 2.8 times less likely to survive for 10 years when compared with patients with VEGF-negative status. Also, patients with T2 disease at time of diagnosis were almost 2 times more likely to suffer local relapse and 1.5 times less likely to survive the following 10 years than patients with T1 disease.

**DISCUSSION**

In our tissue microarray of 123 patients with early laryngeal cancer treated with primary radiotherapy, we found that VEGF positivity significantly predicted poor overall survival. Although the current study found that VEGF positivity was not significantly associated with local relapse in the univariate model (RR 1.32; 95% CI, 0.64–2.24; \(P = .40\)) or in the multivariate model after adjusting for other variables (RR 1.20; 95% CI, 0.46–2.46; \(P = .66\)), there was a trend toward higher local relapse in VEGF-positive tumors. VEGF positivity proved to be a significant predictor of overall survival in the univariate analysis (RR = 1.62; 95% CI, 0.99–2.42; \(P = .05\)) and maintained significance in the multivariate analysis (RR, 2.79; 95% CI, 1.49–4.95; \(P = .002\)).

Age and T classification were also significant predictors of local relapse and overall survival in multivariate analysis. The effect of older age (\(\geq 60\) years) on overall survival is consistent among other studies of a similar cohort.\(^{27}\) In a correlation of VEGF with other prognostic factors, VEGF was associated with higher (T2) clinical stage (Table 2). A similar finding was reported in a retrospective series by Kyzas et al, in which VEGF-positive phenotype was associated with higher clinical stage and worse overall survival.\(^{28}\) As expected, higher T classification (T2) in our study also predicted a relative risk of about 1.5 times that of T1 stage for poorer local disease control \((P < .05)\) and poorer 5-year overall survival \((P < .05)\). Several other studies have demonstrated similar outcomes for higher T-classification laryngeal disease.\(^{8,29,30}\)

Although this is a relatively large series of patients treated uniformly for early stage laryngeal cancer, the number of events was relatively low. A significant limitation of the current study is that information on actual cause of death was limited. With only 5 of 44 patients with evidence of disease at the time of death, it was difficult to determine the cause-specific or distant metastasis-free survival in this study. Additional information concerning causes of death was unavailable in the patient registry, thus we could not distinguish cause-specific survival in this study, thereby limiting interpretation of the prognostic importance of VEGF status. Although VEGF expression appears to be related to overall survival, the lack of information on actual cause of death (ie, disease related or not disease related), does not preclude that VEGF expression is a surrogate marker for other causes of death not related to the primary tumor characteristics. Other associations, such as carcinogen exposure (eg, smoking) and subsequent development of VEGF-overexpressed tumors, could not be evaluated for poorer cause-specific survival, which might have explained the mechanism for poor overall survival. Therefore, although the correlation of VEGF with overall survival is noteworthy, the biological significance of this association remains uncertain.

Although there appears to be a trend toward VEGF expression and local relapse, further assessment of survival rates and local control rates may be possible with larger data sets on patients. A stronger correlation between disease recurrence, VEGF expression, and overall survival would strengthen the argument that VEGF expression in the primary tumor was of true prognostic and therapeutic significance. Thus, to validate our current findings, future studies with larger numbers of patients and a higher number of events may elucidate, in a causative fashion, a relation between poor local control and overall survival.

Our study is in agreement with a recent meta-analysis of HNSCC patients that found relative risk of death to be approximately 2-fold higher in VEGF-positive tumors.\(^{29}\) Interestingly, there was significant “between-study” heterogeneity in assessment of VEGF overexpression. Although only 1 study in this meta-analysis included patients with a similar disease subsite (glottic and supraglottic)\(^{31}\) to the cohort followed in our study, larger studies seemed to provide more conservative estimates of the actual prognostic value of VEGF. In 1 study, VEGF positivity was defined as at least moderate staining in at least 20% of tumor cells.\(^{20}\) Our study used strong staining and in at least 25% of tumors cells as a marker of VEGF positivity. If our study used a threshold of moderate staining for VEGF positivity, prognostic value would be lost. Coupled with our finding that VEGF is associated with later stages (T2) of laryngeal cancer, it may be that more prominent VEGF overexpression is a more appropriate marker to predict outcome in early stages of disease.

In a study of VEGF expression in oral and oropharyngeal cancer, VEGF-positive tumors were more likely to recur locally and distantly, and VEGF positivity was the most significant predictor of poor disease-free survival and overall survival.\(^{19}\) Implied in that study was the use of VEGF as a surrogate marker of
radioresistance and subsequent locoregional failure. Conflicting evidence was reported by Homer et al, who found no difference in VEGF expression between radioresistant and radiosensitive T1 and T2 glottic tumors.\textsuperscript{32} Conflicting opinions on the validity of VEGF as a consistent molecular marker in HNSCC and laryngeal neoplasms may be due to several issues, including heterogeneous population inclusion criteria, uncontrolled independent risk factors, different groups of primary tumor sites, various antibody markers used for immunohistochemical staining, and different patterns of tissue assessment. In relation to our work herein, limited correlation was found between VEGF expression and local relapse, but VEGF level was a predictor of overall survival outcome and perhaps more aggressive disease.

The loss of p53 activity and subsequent uncontrolled cell-cycle growth without arrest and repair of damaged DNA has been established in laryngeal neoplasms.\textsuperscript{33} Watanabe et al found EGFR status to be an independent predictor of local recurrence-free survival but only in patients with T2, T3, or T4 laryngeal neoplasms.\textsuperscript{34} Recent randomized clinical trials combining C225 anti-EGFR antibodies (Cetuximab) with radiotherapy have shown promising locoregional control and reduction in mortality for locally advanced HNSCC.\textsuperscript{35} In the current study, other molecular markers such as EGFR and p53 did not correlate with local relapse or overall survival.

The vascular network that promotes metastatic disease and subsequent poor local and distant relapse rates is strongly associated with VEGF protein expression.\textsuperscript{36} Early laryngeal cancer, which is primarily treated by radiation therapy, provides a good medium for studying the effects of hypoxia-induced VEGF expression and treatment outcomes. As opposed to other HNSCC studies that examined VEGF in a heterogeneous population of tumors, our study included a homogenous cohort of patients with T1-2, node-negative disease of the larynx who were treated in a uniform fashion with primary radiation therapy. Because the tumors examined were of similar disease characteristic, VEGF may be a valid, reproducible prognostic tool.

In addition to its utility as a prognostic tool, VEGF is also the target of molecular pharmacotherapy such as bevacizumab (Avastin). Significantly longer overall survival and progression-free survival times were observed when bevacizumab was added to chemotherapy alone in phase III, randomized clinical trials in metastatic colorectal cancer.\textsuperscript{37} In HNSCC, monoclonal antibodies that target VEGF may become an exciting strategy for adjuvant therapy, especially when different angiogenesis inhibitors become available.

As demonstrated in the current study, VEGF status plays an uncertain role in local control but may be an important factor in predicting overall prognosis, and appropriate clinical decisions may be made on the basis of this molecular classification. Further evaluation of outcomes in VEGF-positive laryngeal cancers treated with primary radiotherapy is warranted in larger, prospective, clinical trials.

REFERENCES


